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EFFECTS OF HEAD TRAUMA AND BRAIN INJURY ON
NEUROENDOCRINOLOGIC FUNCTION

ANNUAL REPORT

Paul D. Woolf, M.D.
Robert W. Hamill, M.D.

October 31, 1986

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3142
University of Rochester Medical Center
Rochester, New York 14642

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Patients with traumatic injury, admitted within 48 hours of their accident were studied to determine the association between the severity of injury assessed by standard techniques and sympathetic nervous system function in order to determine whether 1) catecholamine levels can be used to predict patient outcome, 2) excessive catecholamine release contributes to morbidity and mortality, and 3) brain injury and/or sympathetic nervous system activation contribute to pituitary dysfunction. During the period of this report 82 patients (170 over the three years of the contact) with head injury were studied of whom 25 had systemic trauma and 2 had spinal cord injuries. The conclusion of the investigation of the catecholamine response to brain injury revealed that in 61 traumatically brain-injured patients studied within 48 hours of injury, norepinephrine levels separated patients into those universally improved (i.e. < 900 pg/ml) and those who were very likely to have minimal or no improvement or who died (> 900 pg/ml). Patients surviving one week had catecholamines which increased progressively as patient outcome worsened. Patients					
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with poor outcomes (persistent vegetative state and death) had significantly higher levels of each of the three catecholamines. Similar significant correlations were present using norepinephrine concentrations and a combination of pupillary responses and patient outcome. Analysis of the interactions of the catecholamines and GCS on Glasgow Outcome Scores, the duration on ventilatory assistance, and length of hospitalization revealed that the catecholamines either enhanced the reliability of the GCS or were predictors independently of their association with GCS.

Using the Injury Severity Scale as an anatomically-based index incorporating systemic as well as brain injury, we were able to demonstrate highly association between the ISS scores and catecholamines in patients with multisystem injury providing that brain injury was also present. Equally severe trauma in the absence of brain injury, yielding ISS scores that were comparable, were not associated with increasing catecholamines.

In the evaluation of the effects of brain injury on pituitary function, two studies were completed. In the first, we demonstrated that the severity of hypogonadism is dependent upon the degree of neurologic impairment, that there is a significant negative correlation between changes in testosterone levels, and finally, that steroid precursors involved in the testosterone, but not in the cortisol, pathways also becomes subnormal.

Investigation of the thyroid dysfunction, which occurs following traumatic brain injury revealed that it is also dependent upon the degree of neurologic impairment and that thyroid function abnormalities reflect ultimate outcome. The significant association with catecholamines suggest a role of sympathetic nervous system activation in causing the thyroid function, which is independent of the generalized stress responses.



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Summary

The final yearly report covers a period from July 1, 1985 through August 14, 1986. The time span of this report has been lengthened modestly to encompass the conclusion of the project. During this period, 82 patients with head injury were studied. In 25 of these, systemic trauma was also present while spinal cord injury was present in 2 other patients. Thirty-one patients with other acute neurologic problems were studied during this interval including: 13 with intracerebral hemorrhage, 8 with spinal cord injury, 7 with CVA's, 2 with subarachnoid hemorrhage and one with anoxic brain injury. Poly-trauma without brain injury was studied in 21 additional patients.

Thus, for the three years of the contract, we have studied 170 patients with traumatic head injury, 70 patients with acute non-traumatic neurologic disease, predominately vascular CNS disorders, and 71 patients with acute non-neurologic disorders including multiple systemic trauma.

The following hormonal determinations were performed during the past year: catecholamines, both free and conjugated, 677; cortisol, 550; ACTH, 100; beta-endorphin, 124; LH, 6; FSH, 6; testosterone, 115; growth hormone, 8; TSH, 73; T₄, 154; T₃, 154; free T₄, 79; leucine enkephalin 106.

Forward

In the conduct of research where humans are the subjects, the investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by 45 CFR 46 (Protection of Human Subjects).

B. Specific Projects

All but one of the studies started under our current contract have been completed; namely, the evaluation of the utility of catecholamines in predicting patient morbidity and mortality in the traumatically brain injured patient and the evaluation of the impact of brain injury on the hypothalamic-pituitary-end organ axes. A major phase of the project, which is currently under statistical review is the correlation of the site and size of CNS lesions, determined by CT scanning, on GCS and catecholamine levels. It is anticipated that this analysis will be completed shortly.

As our patient base increased in size, attention turned increasingly to our first Specific Aim; namely, investigation of the sympathetic nervous system response to traumatic brain injury, while our investigation of the pituitary and gonadal responses to head trauma and acute illness was brought to a successful conclusion.

1. Catecholamines as markers of injury severity.

Norepinephrine, epinephrine and dopamine levels were measured in 61 traumatically brain injured patients within 48 hours of injury. As previously demonstrated, each catecholamine correlated with the admission GCS. In 21 patients GCS 3/4 on admission with norepinephrine levels below 900 pg/ml, all improved to >11, while 12 out of 15 NE levels >900 pg/ml remained GCS 3 to 6 or died. Moreover, in patients who survived the week, catecholamines increased progressively and significantly as the Glasgow Outcome Scale worsened from good

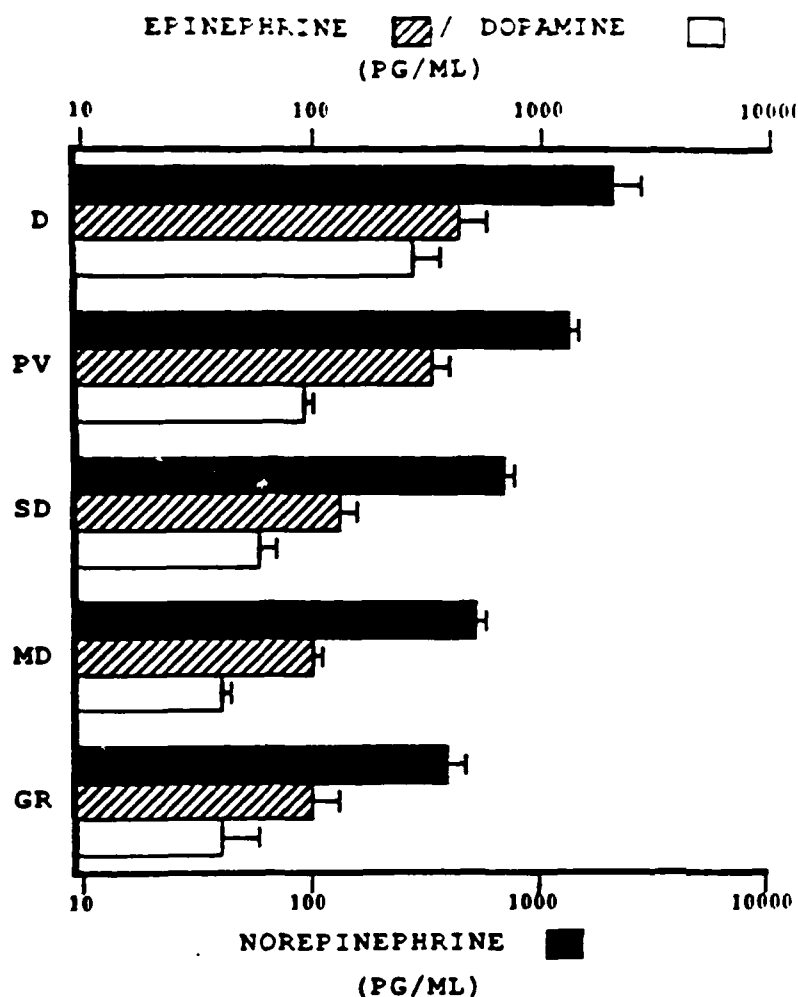


Fig. 1.

recovery through death (Fig. 1). Logistic regression analysis of poor outcome (persistent vegetative state and death) revealed significant differences in each of the three catecholamines. Analysis of the pupillary responses and catecholamine levels revealed significant differences as the patients went from good outcome with reactive pupils, through bad outcome with reactive pupils and finally to bad outcome with nonreactive pupils (norepinephrine levels of 561, 1252 and 2,046 pg/ml, respectively). These concentrations were highly significantly different. In 54 patients who survived at least a week, significant correlations were present between the length of hospitalization and NE and E levels. There were a similar correlations between NE and E levels and the duration of ventilatory assistance. Finally, analysis of the interactions of the catecholamines and GCS on GOS, the duration of ventilatory assistance and length of hospitalization revealed that the catecholamines either enhanced reliability

of the GCS or they were predictors independently of their association of the GCS. The demonstration of the interactions of norepinephrine and GCS on the GOS is provided in Fig. 2 where the linear predictor is given by the equation: linear predictor = $1.9 - 0.056$

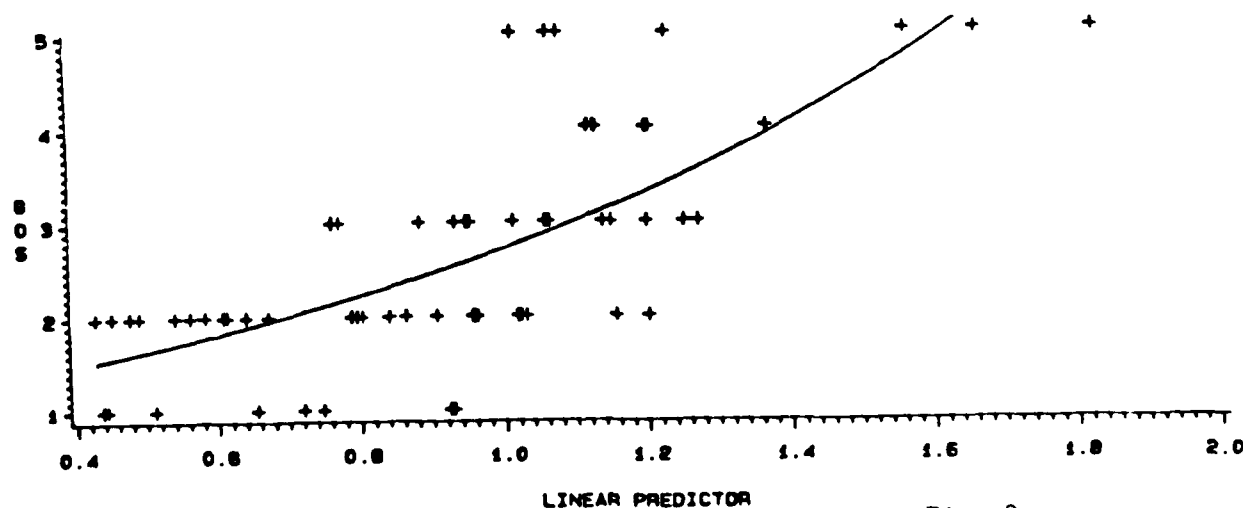


Fig. 2.

GCS + 0.000168 NE. The GOS scores are: 1, good recovery; 2, moderate disability; 3, severe disability; 4, persistent vegetative state; and 5, death. Using this analysis, the presence of a GCS of 3 and a high norepinephrine level predicts a poor outcome, while another patient with the same GCS, but much lower norepinephrine levels (i.e. 800 pg/ml) has a value for the linear predictor which would predict a better outcome. A similar linear predictor would also be present with a GCS of 6 and a norepinephrine level of 2,000 pg/ml. Thus, it is the interaction of these two parameters that better define ultimate patient morbidity and mortality than either one alone.

Up until now, we have used the GCS as the principal index for determining patient morbidity. We have also begun to use the Injury Severity Scale, based on the AIS 80 ratings, to look at the interactions of an index based upon the anatomic site of injury with an associated injury weight and the sympathetic nervous system response. There are highly significant associations between the ISS scale and patients with multisystem injury providing brain injury is also present. Equally severe trauma, but in the absence of brain injury, yielding ISS scores that are comparable, are not associated with increasing catecholamines. These data provide further support for the hypothesis that brain injury per se activates the sympathetic nervous system response in a graded manner.

One of the ways which we are trying to assess the cause of CNS activation in brain injured patients is through a detailed radiologic analysis of the extent and site of brain lesions as determined by CT scanning. All patients that have had CT scans and admission catecholamines have been read blindly by our neuroradiologist and coded onto extensive forms. These are currently being analyzed by our statistician, and we hope to have the results of this analysis shortly.

2. Studies of pituitary function.

A. Gonadal studies.

Our investigation of the transient hypogonadotropic hypogonadism occurring in the post-injury setting is complete. In our previous study we demonstrated that patients have rapid falls in gonadotropin levels which are detectable within 12 hours and maximal by three or four days after injury. During the past year, we have completed the study on interactions of traumatic brain injury with gonadal steroidogenesis and with sympathetic nervous system activation. We found that the severity of the hypogonadism is dependent on the magnitude of the neurologic impairment since patients who remain comatose through day four have significant lower levels of testosterone than those who awakened.

Our data also demonstrated the heterogeneity of the alterations in the various steroid responses. Cortisol remained elevated while testosterone and its precursors, 17-hydroxyprogesterone became suppressed. Androstenedione which is secreted by both the adrenal and testis is similarly affected. Finally, we were able to show highly significant correlations between testosterone levels on Day 4 and admission norepinephrine levels. Thus, we were able to demonstrate that severe traumatic brain injury leads to hypogonadotropic hypogonadism which effects testosterone and its precursors. The magnitude of the hormonal dysfunction is dependent upon the severity of the neurologic insult and the correlation between the changes in testosterone and admission catecholamines suggest that the sympathetic nervous system may play a role in mediating these changes.

B. Pituitary thyroid disease.

Acute illness is well known to affect thyroid function. However, there are few studies correlating the severity of the underlying medical problem with the degree of test abnormality and little is known about its etiology. For these reasons we investigated the impact of traumatic brain injury in 54 patients and studied the relationships between changes in thyroid function tests measured on admission and again 4 days post accident (T_4 , free T_4 , T_3 , reverse T_3 [rT_3] and TSH levels) and neurologic function as assessed by the Glasgow Coma Score (GCS), the catecholamines NE and E and cortisol concentrations. In all patients T_3 fell 28.4 ± 7.3 (SE) ng/dl ($p < 0.004$), but other mean thyroid parameters did not change. Significant correlations were present between the day 4 GCS and concomitant T_4 ($r=0.46$, $p < 0.001$), free T_4 ($r=0.52$, $p < 0.02$) and T_3 ($r=0.45$, $p < 0.001$) levels, i.e.; those with the greatest neurologic dysfunction had the lowest hormone levels. rT_3 and TSH remained unchanged throughout the study even in the most severely affected patients and TSH responded normally in the two who received TRH (500 ug). Significant correlations were also present between day 4 T_4 ($r=-0.49$, $p < 0.002$) and T_3 ($r=-0.44$, $p < 0.01$) levels and ultimate patient outcome, ranging from good recovery through death. The thyroid data were comparable in patients with ($N=22$) or without ($N=32$) Dilantin treatment. Highly significant correlations were present between day 4 T_4 levels and admission NE ($r=-0.39$, $p < 0.004$) and E ($r=-0.40$, $p < 0.003$) and between day 4 T_3 and NE ($r=-0.33$, $p < 0.02$) and E ($r=-0.28$, $p < 0.04$), but not between free T_4 , rT_3 and TSH concentrations. There was no association between admission or concomitant cortisol levels and thyroid function on day 4 ($N=41$) and patients treated with high dose dexamethasone ($N=13$) had values comparable to those who were not.

Thus, a gradient of thyroid dysfunction is present in patients suffering from traumatic brain injury, which is dependent upon the degree of neurologic impairment and which reflects ultimate outcome. The significant association with catecholamine levels suggests a role for sympathetic nervous system activation in its causation, independent of a generalized stress response, since there is no correlation of thyroid test abnormality with the degree of adrenocortical secretion.

Papers, Abstracts or Presentations Resulting From the Final Year of Support by This Contract.

Papers

1. Woolf PD, RW Hamill, JV McDonald, LA Lee, M Kelly: Transient Hypogonadotropic and Hypogonadism Caused by Critical Illness, *J Clin Endocrinol Metab* 60:444-457, 1985.
2. Lee LA, Mooney RA, Woolf PD: Clinical Utility of Measuring Free Thyroxin and Free Triiodothyronine in Serum of Critically Ill Patients by Ultrafiltration. *Clin. Chem.* 32:797-800, 1986.
3. Hamill RW, PD Woolf, JV McDonald, LA Lee, M Kelly: Catecholamines Predict Outcome of Traumatic Brain Injury, *Annals of Neurology*, in press.
4. Woolf PD, RW Hamill, JV McDonald, LA Lee, M Kelly: Transient Hypogonadotropic Hypogonadism After Head Trauma: Effects on Steroid Precursors and Correlation with Sympathetic Nervous System Activity, *Clinical Endocrinology* 25:265, 1986.
5. Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV: The Predictive Value of Catecholamines in Assessing Outcome in Traumatic Brain Injury. Submitted for publication.

Presentations:

1. Woolf PD, Hamill RH, McDonald JV, Lee LA, Kelly M: Transient Hypogonadotropic Hypogonadism After Head Trauma: Correlation With Sympathetic Nervous System. *Endocrine Society*, 1985.
2. Woolf PD, Hamill RW, McDonald JV, Lee LA: Admission Catecholamine Levels as Physiologic Markers of Outcome in Traumatic Brain Injury. *American Association of Neurological Surgeons*, 1986.
3. Woolf PD, Hamill RA, McDonald JV, Lee LA: Adreno-Medullary and Adreno-Cortical Responses Correlate with Severity of Traumatic Brain Injury. *Endocrine Society*, 1986.